REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 55-85 are pending and currently under examination in the application. Notwithstanding the grounds for any rejection, and without prejudice to pursuing the encompassed subject matter in a related divisional, continuation, or continuation-in-part application, by the present amendment, claims 63-77 are canceled, and claim 55 is amended to more particularly point out and distinctly claim certain embodiments of the Applicants' invention. No new matter is added by the present amendment. Support for the amendment can be found in the specification, for example, on page 8, lines 27-29; and in the claims.

Request to Withdraw the Finality of the Rejection

Applicants respectfully request that the Examiner withdraw the finality of the rejection in the instant Action. In particular, Applicants note that before a final rejection is in order, a clear issue should be developed between the Examiner and Applicants. M.P.E.P. § 706.07. Indeed, an Applicant who is seeking to define his or her invention in claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the Examiner to that end, and not be prematurely cut off in the prosecution of his or her application. *Id.*

Here, the Examiner and the Applicants have not developed a clear issue in relation to the subject matter of claims 78-85. In explanation, Applicants note that the Response of October 25, 2007, contained new claims 78-85, encompassing methods of generating a cell of a blood vessel, which claims apparently received no substantive examination on the merits. For example, the Examiner asserts in the instant Action that the "issue is not the ability of MSCs to differentiate into cardiomyocytes and endothelial cells" (*see* the Action, page 4). Even assuming, *arguendo*, that the ability of MSCs to differentiate into endothelial cells is not relevant to methods of generating a blood vessel, as in claims 55-62, this ability *should* represent a relevant issue in relation to claims 78-85. Applicants, therefore, feel that the subject matter encompassed by claims 78-85 failed to receive substantive evaluation on the merits, apart from the rest of the pending claims.

As such, since the Applicants have not had the opportunity to develop a clear issue between the Examiner and Applicants with regard to the subject matter of claims 78-85, Applicants submit that the instant Final Rejection is premature, and respectfully request reconsideration and withdrawal of the same.

Claim Objections

The Examiner objects to claim 70 as allegedly being a substantial duplicate of claim 56, and further applies this objection to claim 79. Notwithstanding the grounds for any rejection, Applicants note that claim 70 has been canceled, rendering moot the Examiner's objection to this claim. With regard to claim 79, Applicants will address this basis for the Examiner's objection upon indication of an allowable claim set in the application.

Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner rejects claims 55-85 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner asserts that the specification is not enabling for generating or repairing any type of blood vessel, including major veins and arteries, or treating any disease associated with a vascular disorder.

Applicants traverse this rejection and submit that the subject matter of the instant claims is commensurate in scope with the specification and the understanding in the art at the time of filing. For one, Applicants respectfully disagree with the Examiner's statement of the issue under discussion, such as on page 4 of the instant Action. In particular, the Examiner asserts, in part, that the issue is not the ability of MSCs to differentiate into cardiomyocytes and endothelial cells, but is whether the administration of a mixed population of stromal cells can generate any type of blood vessel in appropriate sites in a controlled manner (*see* the Action, page 4). Even assuming, *arguendo*, that the Examiner's position ever represented an appropriate statement of the issue, Applicants note, by present amendment, that the instant claims encompass methods of generating a cell of a blood vessel, rendering moot the Examiner's above-noted issue statement. Indeed, Applicants would like to respectfully point out that the Amendment and Response of October 25, 2007 contained claims encompassing methods of generating a cell of a

blood vessel, which subject matter the Examiner failed to specifically address in the instant Action.

Nonetheless, as disclosed in the specification and understood in the art at the time of filing, Applicants submit that a person skilled in the art can practice the full scope of the subject matter of the instant claims using nothing more than routine experimentation. Indeed, routine experimentation does not constitute undue experimentation under 35 U.S.C. § 112, first paragraph. *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998).

The specification teaches a person skilled in the art how to make and use the full scope of the presently claimed subject matter without undue experimentation, which scope encompasses administering culture expanded bone marrow stromal cells to a mammal, wherein the cells differentiate into cells of a blood vessel in the mammal, thereby generating the cell of a blood vessel. For example, as previously made of record, the specification provides exemplary guidance on isolating, enriching, and expanding MSCs as recited in the claims (*see, e.g.,* page 31, line 24 through page 32, line 10). A person skilled in the art can determine whether donor stromal cells are matched (*i.e.,* syngeneic, autologous, or allogeneic) according to routine techniques well-known in the art (*see, e.g.,* page 29, lines 15-18 of the specification). The specification, therefore, teaches a person skilled in the art how to *make* culture expanded, donor MSCs for use with the present methods.

As also previously made of record, the specification teaches a person skilled how to *use* MSCs, as presently claimed, using nothing more than routine experimentation. For instance, the specification teaches by example that MSCs may be administered to a mammal systemically, such as by intravenous injection, and provides exemplary dosages for administration (*see, e.g.,* page 30, line 1 through page 33, line 4; and page 32, lines 15-17 and lines 25-27). In addition, Both Example 1 and Pereira *et al.* provide exemplary guidance in determining the fate of MSCs administered to a mammal, and in particular demonstrate how to determine whether administered MSCs differentiate and/or associate with a given tissue, such as a blood vessel (*see, e.g.,* page 31, line 7 through page 34, line 17; and Pereira *et al., Proc. Natl. Acad. Sci. USA*, May 1995, Vol. 92, pp. 4857-4861, which is incorporated by reference into the instant application on page 36, lines 18-20). According to the techniques outlined in the specification and known in the art, a person skilled in the art may routinely assess whether an

MSC differentiates into a cell of a blood vessel, such as an endothelial vascular cell, using known markers for endothelial cells. Following MSC administration, a person skilled in the art can, therefore, use the guidance provided in both the specification and the art to routinely demonstrate whether MSCs differentiate into a cell of a blood vessel, as recited in the instant claims.

Applicants note that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). Here, to put it simply, Applicants have clearly disclosed at least one method for administering culture expanded MSCs to a mammal, and have further disclosed at least one method for determining whether those cells generate a cell of a blood vessel, using nothing more than routine experimentation. This disclosure reasonably correlates with the scope of the instant claims, as amended herewith, and indeed, reads almost exactly on the scope of these claims.

As also made of record, a person skilled in the art would have reasonably expected from the specification and the art at the time of filing that MSCs are capable of generating a cell of a blood vessel. For instance, as recognized by the Examiner, the specification states that stromal cells will develop into cells of a blood vessel (*see, e.g.,* page 8, lines 27-29). The specification also shows that cultured MSCs can serve as stem-cell-like precursors of mesenchymal tissues (*see, e.g.,* page 42, lines 16-19), which a person skilled in the art knows to include blood vessel tissues and the cells therein, such as endothelial cells. Applicants feel the need to point out that a specification *must* be taken as in compliance with the enabling requirement of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein. *In re Brana* 51 F.3d 1560, 1566 (Fed. Cir. 1995), citing *In re Marzocchi,* 439 F.2d 220, 223 (CCPA 1971) (emphasis in original). Here, the Examiner has failed to establish a reason to doubt the objective truth of the specification statement that MSCs can develop into cells of a blood vessel, as recited in the instant claims. Indeed, as previously made of record and recognized by the Examiner, the references cited by the Examiner support the objective truth of the statement that MSCs can generate cells of a blood vessel, including cardiomyocytes and endothelial cells (*see, e.g.,* Nagaya *et al.*, first and second column, p. H2675; and the Action,

page 5). Since the burden lies on the Examiner to prove otherwise, and since the Examiner has not satisfied that burden, Applicants submit that a person skilled in the art at the time of filing would have accepted that MSCs could generate a cell of blood vessel, as presently claimed.

Moreover, despite the Examiner's assertion that post-filing evidence cannot supplement an Applicants' disclosure, post-filing evidence can be used to *substantiate* the accuracy of a statement already in the specification, especially when the disclosure therein was accomplished by following the teachings of the specification. *See* 51 F.3d at 1567; and *Hopkins,* 152 F.3d at 1360. Here, the statement that MSCs can develop into a cell of a blood vessel was already in the specification at the time of filing, and, as previously made of record, post-filing references, such as Nagaya *et al.*, *substantiate* the accuracy of this statement by demonstrating that even a mixed population of systemically administered MSCs develop into cells of a blood vessel (*i.e.,* vascular endothelial cells), as presently claimed. Accordingly, in combination with the specification disclosure, which, as discussed herein, teaches a person skilled in the art how to make and use the presently claimed subject matter, Applicants may properly utilize these post-filing references to *substantiate* the enablement of the instant claims under § 112.

With further regard to the Examiner's assertions relating to possible side effects, such as whether systemic administration would introduce stem cells to undesired locations wherein subsequent differentiation could complicate, rather than treat the disease state (*see* the Action, pages 4 and 8), Applicants respectfully disagree not only with the Examiner's interpretation of the state of the art with regard to the same, but with Examiner's reliance on this basis for an enablement rejection. In the previous Response, Applicants clearly articulated their position on the of the state of the art, especially with regard to the teachings of post-filing references such as Nagaya *et al.* and Zisch *et al.*, which need not be reiterated here. Rather, Applicants further note, more generally, that stem cell containing transplants have been well-utilized in the therapeutic arts despite the Examiner's concern that such administration may introduce stem cells to undesired locations, such as by causing the vascularization of dormant tumors (*see* the Action, page 8). Indeed, merely by way of example, Zimmerman *et al.* report at the time of filing that patients not only tolerate infusions of culture expanded CD34-positive stem cells *without problems*, but achieve engraftment. *J Hematother.* 4:527-9, 1995. Accordingly, despite the Examiner's emphasis on speculative risks, a person skilled in the stem

cell-related therapeutic arts *at the time of filing* was willing to accept the therapeutic potential of stem cell transplantation methodologies, such as with the MSCs claimed herein.

Applicants also respectfully disagree with the Examiner's reliance on this basis for an enablement rejection. Indeed, the Examiner on the one hand asserts that human testing has not been required (*see* the Action, page 7), but on the other hand applies a standard of safety that, essentially, can only be proven by substantial clinical testing. Applicants respectfully note that the specification need not demonstrate that the invention is completely safe, such as by showing that MSCs will not calcify in the heart or vascularize dormant tumors. M.P.E.P. § 2164.01(c). Indeed, as previously made of record, 35 U.S.C. § 112, first paragraph, does not require an Applicant to demonstrate that a therapeutic method is either safe or fully effective. *See, e.g., In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995), citing *Scott v. Finney,* 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full *safety* and *efficacy*...is more properly left to the Food and Drug Administration (FDA)") (emphasis added). Here, the Examiner relies on speculative assertions as to the safety of administering MSCs, whether purified or partially enriched, as a basis to reject the instant claims for alleged lack of enablement. The PTO, however, is not responsible for determining the safety or efficacy of a given therapeutic method, since this is the role of the FDA. *Id.* Accordingly, the Examiner's relies inappropriately on this particular basis in rejecting the instant claims under 35 U.S.C. § 112, first paragraph.

Similarly, Applicants' respectfully disagree with the Examiner's emphasis on the asserted need for continued research to fully explore the therapeutic potential of MSCs. Indeed, the specification need not fully flesh out the therapeutic potential of any given invention, such as precise dosages, modes of administration, or, as above, safety issues. As previously made of record, the enablement requirement under § 112 clearly contemplates the need for further experimentation, as long as that experimentation is merely routine, and even contemplates the enablement of therapeutic methods or treatments that may eventually provide no therapeutic value at all. *See, e.g., In re Angstadt,* 537 F.2d 498, 503 (CCPA 1976); and *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961). In view of the specification disclosure and the understanding in the art, as discussed herein, Applicants respectfully submit that the Examiner's articulated bases for rejecting the instant claims fails to reflect this proper standard under 35 U.S.C. § 112, first paragraph, enablement.

In view of the present amendments and the above remarks, Applicants submit that a person skilled in the art can practice a method of generating a cell of a blood vessel, as presently claimed, without undue experimentation. Applicants, therefore, submit that the instant claims satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. As such, Applicants respectfully request reconsideration and withdrawal of this rejection to the claims.

Obviousness Type Double Patenting

The Examiner provisionally rejects claims 55-85 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 55-70 of co-pending Application No. 10/423,232, in addition to claims 17-28 of co-pending Application No. 10/844,235.

Applicants traverse this rejection and submit that the instant claims are patentable over the claims in both Application No. 10/423,232 and Application No. 10/844,235. Nonetheless, Applicants note that Application No. 10/423,232 has been abandoned, rendering moot this basis for the Examiner's rejection.

In addition, Applicants note that when a "provisional" nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the earlier-filed of the two pending applications, while the later-filed application is rejectable on other grounds, the Examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. M.P.E.P. § 804 (I)(B)(1).

Here, the priority filing date of the instant application is earlier than the priority filing date of Application No. 10/844,235. Accordingly, if this provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the present application after entry of the present Amendments and consideration of the remarks herein, Applicants respectfully request withdrawal of this provisional rejection in accordance with M.P.E.P § 804 (I)(B)(1) so that the present application may proceed to allowance.

Applicants respectfully submit that all the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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